

# Very rapid effect of pitavastatin on microvascular function in comparison to rosuvastatin: reactive hyperemia peripheral arterial tonometric study

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**Background:** It has been reported that pitavastatin improves endothelial function faster than other statins. Recently introduced reactive hyperemia peripheral arterial tonometry (RH-PAT) provides objective and quantitative assessment of peripheral microvascular function.

**Purpose:** This study aimed to investigate whether peripheral microvascular function improved 2 hours after pitavastatin in subjects with coronary artery disease (CAD) using RH-PAT, and the results were compared with those of rosuvastatin.

**Methods:** This study included 94 subjects with CAD, assigned to a group given 2 mg of pitavastatin (n = 36), a group given 2.5 mg of rosuvastatin (n = 38), and a control group (n = 20). RH-PAT examinations were performed before and 2 hours after statin administration.

**Results:** The RH-PAT index increased 2 hours after pitavastatin administration from  $1.82 \pm 0.45$  to  $2.16 \pm 0.62$  ( $P = 0.02$ ), whereas there were no differences in the RH-PAT index in the rosuvastatin group ( $1.79 \pm 0.71$  to  $1.91 \pm 0.53$ ,  $P = 0.09$ ) and the control group ( $1.68 \pm 0.36$  to  $1.84 \pm 0.58$ ,  $P = 0.4$ ). No significant changes were observed at 2 hours in serum cholesterol levels in each group.

**Conclusion:** The present study demonstrated that peripheral microvascular function improved 2 hours after a single clinical dose of pitavastatin, but not after rosuvastatin.

**Keywords:** coronary artery disease, statin, microvascular function

## Introduction

Evidence from several large, randomized, controlled trials has demonstrated that the decrease in the serum cholesterol concentration produced by the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) reduces the mortality of subjects with coronary artery disease (CAD).<sup>1,2</sup> Previous studies have confirmed that statins have pleiotropic effects, including improvement of endothelial function, and that effects other than cholesterol reduction may contribute to reduction of cardiovascular complications.<sup>3</sup> These putatively cholesterol-independent effects may be exerted more rapidly than cholesterol lowering itself, ranging from 1 day to several months.<sup>4-8</sup> Previous reports have shown that pitavastatin may improve endothelial function faster than other statins.<sup>9,10</sup> Therefore, we hypothesized that pitavastatin, but not other statins, improves microvascular function within several hours in subjects with CAD.

Reactive hyperemia peripheral arterial tonometry (RH-PAT) has recently been introduced to evaluate peripheral microvascular function.<sup>11-14</sup> RH-PAT is designed to measure volumetric changes in the fingertip by using a probe to quantify pulse amplitude in response to reactive hyperemia. This technique has been reported to be useful in identifying cardiovascular risk factors. Considering it is noninvasive and

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less operator- and observer-dependent, this method may have the potential to detect subtle differences in serial measurements of microvascular function. This study therefore aimed to investigate the very rapid effects (within 2 hours) of pitavastatin on peripheral microvascular function using RH-PAT in subjects with CAD and compare them with those of rosuvastatin.

## Methods

### Study population

There were 94 study subjects with hemodynamically stable CAD ( $68 \pm 12$  years of age, 73 males) who had serum low-density lipoprotein (LDL)-cholesterol  $\geq 100$  mg/dL, and/or LDL/high-density lipoprotein (HDL)-cholesterol ratio  $\geq 2$ . CAD was defined as  $\geq 50\%$  organic stenosis based on the classification by the American Heart Association on coronary angiography in at least one branch of the coronary artery. Subjects were excluded if they had a history of statin therapy, valvular heart disease, severe hepatic disease (history of liver cirrhosis or alanine aminotransferase  $> 2.5$  times upper normal), or renal failure (serum creatinine  $> 2.0$  mg/dL). The study subjects were assigned to the following three groups: (1) 2 mg of pitavastatin, (2) 2.5 mg of rosuvastatin, and (3) placebo (control group). This study was approved by the Institutional Review Board of the Osaka Ekisaikai Hospital, and all subjects gave their informed consent.

### Protocol

A quiet, temperature-controlled ( $24^{\circ}\text{C}$ – $27^{\circ}\text{C}$ ) room was used for the RH-PAT test. Subjects underwent RH-PAT examinations before and 2 hours after statin intake in the pitavastatin and rosuvastatin groups. Blood samples were taken immediately before each RH-PAT examination. These examinations were performed more than 3 hours after meals and after 30 minutes of rest lying down. In the control group, the RH-PAT tests were performed before and after 2 hours of rest without statin treatment, to investigate the effect of repeated RH-PAT tests on the results.

### RH-PAT examination

RH-PAT was performed using ENDO-PAT 2000 (Itamar Medical, Caesarea, Israel). Specially designed finger probes were placed on the middle finger of each subject's hand. These probes consisted of a system of inflatable latex air cuffs connected by pneumatic tubes to an inflating device controlled through a computer algorithm. Pulsatile volume changes of the distal digit induced pressure alterations in the finger cuff, which were sensed by pressure transducers.

Subjects were instructed to remain at rest for 5 minutes to obtain a baseline measurement. After 5 minutes of baseline recording, a blood pressure cuff was inflated to 60 mm Hg above systolic pressure or at least 200 mm Hg in the test arm. After 5 minutes of occlusion, the cuff was rapidly deflated, with PAT tracings being recorded for a further 6 minutes. The ratio of the PAT signal after cuff deflation compared with baseline was calculated through a computer algorithm automatically normalizing for the baseline signal and indexed to the contralateral arm.

### Statistical analysis

Values are expressed as mean  $\pm$  standard deviation. Comparisons of the RH-PAT index and laboratory and hemodynamic data before and after statin administration were performed using the Mann–Whitney U test. The chi-square test was used for comparison of categorical variables. One-way analysis of variance followed by a post-hoc Bonferroni test was used to compare the three groups (pitavastatin, rosuvastatin, and control groups). Differences were considered significant at  $P < 0.05$ .

Inter- and intra-observer variabilities of RH-PAT examination were examined in 10 healthy subjects (8 males, mean age  $31 \pm 5$  years) who had no history of cardiac disease or risk factors. Inter-observer variability for RH-PAT examination was analyzed with two independent blinded observers. Intra-observer variability was analyzed with the same observer at two different time points. The results were analyzed by both least squares fit linear regression analysis and the Bland–Altman method.

## Results

Of the 94 subjects, 36 subjects were assigned to the pitavastatin group, 38 subjects to the rosuvastatin group, and 20 subjects to the control group. The clinical characteristics of the three groups are summarized in Table 1. There were no correlations between baseline RH-PAT index and medications, including beta-blockers, calcium channel blockers, angiotensin converting enzyme inhibitors or angiotensin receptor blockers, and aspirin, as shown in Figure 1. There was no significant difference in the baseline value of the RH-PAT index among the three groups:  $1.82 \pm 0.45$  in the pitavastatin group,  $1.79 \pm 0.71$  in the rosuvastatin group, and  $1.68 \pm 0.36$  in the controls ( $P = 0.6$ ). Further, the baseline laboratory parameters and hemodynamics did not differ significantly among the three groups (Figure 2).

The RH-PAT index increased significantly 2 hours after pitavastatin administration, from  $1.82 \pm 0.45$  to  $2.16 \pm 0.62$  ( $P = 0.02$ ), as shown in Figure 2. However, there were no

**Table 1** Clinical characteristics of the pitavastatin, rosuvastatin, and control groups

	Pitavastatin (n = 36)	Rosuvastatin (n = 38)	Control (n = 20)	P-value
Age, years	68 ± 12	63 ± 12	70 ± 11	0.08
Sex (male), n (%)	30 (83%)	29 (76%)	14 (70%)	0.5
Hypertension, n (%)	27 (75%)	31 (82%)	17 (85%)	0.6
Hyperlipidemia, n (%)	19 (53%)	20 (53%)	7 (35%)	0.4
Diabetes, n (%)	17 (47%)	18 (47%)	8 (40%)	0.8
Body mass index, kg/m <sup>2</sup>	23.6 ± 3.9	23.2 ± 4.1	22.8 ± 4.6	0.5
Previous history of MI, n (%)	8 (22%)	8 (22%)	5 (25%)	0.9
Previous history of coronary revascularization, n (%)	20 (56%)	15 (39%)	11 (55%)	0.3
Medication				
Beta-blockers, n (%)	10 (28%)	9 (24%)	5 (25%)	0.9
Calcium channel blockers, n (%)	20 (56%)	13 (34%)	8 (40%)	0.2
ACEI or ARB, n (%)	22 (61%)	28 (74%)	12 (60%)	0.4
Aspirin, n (%)	24 (67%)	22 (58%)	11 (55%)	0.6

**Note:** Values are mean ± SD.

**Abbreviations:** ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blockers; MI, myocardial infarction.

differences in the RH-PAT index in the rosuvastatin group ( $1.79 \pm 0.71$  to  $1.91 \pm 0.53$ ,  $P = 0.09$ ) and the control group ( $1.68 \pm 0.36$  to  $1.84 \pm 0.58$ ,  $P = 0.4$ ). Moreover, there were no significant differences in any laboratory parameters before and after statin intake in each group.

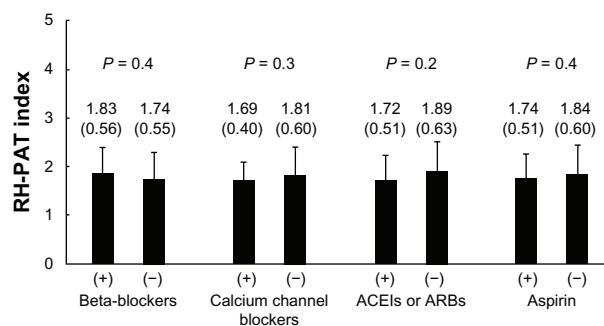
Excellent correlations were observed for inter-observer and intra-observer variabilities of RH-PAT examination. Values were  $r = 0.92$  and  $r = 0.95$  for the RH-PAT index. From the Bland–Altman method, inter- and intra-observer variabilities for the RH-PAT index were 0.04 and 0.06, respectively.

## Discussion

### Advantages of RH-PAT over flow-mediated dilation (FMD)

FMD of the brachial artery is a widely used method for the study of endothelial function in clinical practice.<sup>15–17</sup>

However, this method requires a certain degree of skill to obtain accurate measurements of brachial artery diameter. Furthermore, sympathetic nervous activity and subsequent hemodynamic changes may affect the FMD result.<sup>15,18</sup> The RH-PAT system has the potential to overcome these shortcomings of the FMD test. This method is an automatic, less operator-dependent, quantitative test for digital volume measurement of the hyperemic response, and by normalizing using the contralateral arm measurement, the effect of hemodynamic changes can be eliminated.<sup>11–14</sup> Importantly, the relationship between or a comparison of the FMD and RH-PAT index needs careful consideration. Some studies have indicated that FMD and RH-PAT index reflect different pathologies of peripheral vascular endothelial function.<sup>19,20</sup> FMD is used to assess large artery reactivity, whereas the RH-PAT index reflects microvascular function. The RH-PAT index has been shown to be at least 50% dependent on endothelial nitric oxide (NO) activity.<sup>21</sup> Therefore, the RH-PAT index may be suitable for assessing subtle differences in serial measurements of microvascular function.



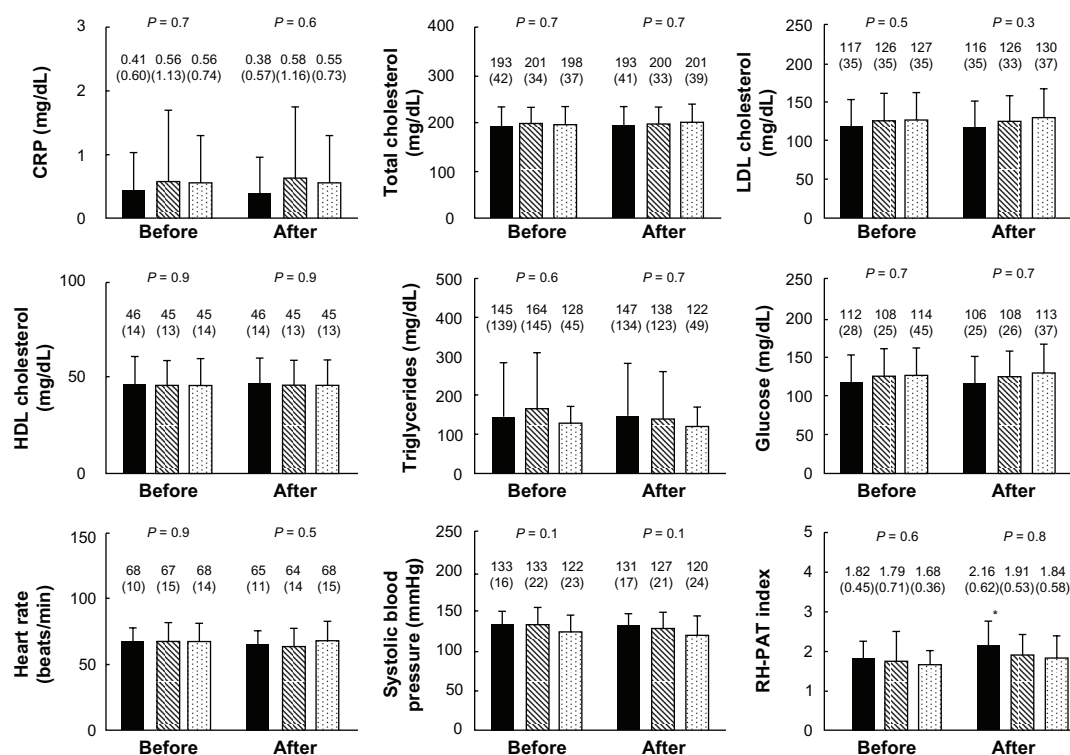
**Figure 1** Baseline RH-PAT index and medications.

**Notes:** Values are expressed as mean (standard deviation).  $P$ -values showed the results of the comparison of RH-PAT index before and after treatment in each medication.

**Abbreviations:** ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; RH-PAT, reactive hyperemia peripheral arterial tonometry.

### Rapid effects of statins on endothelial function

Previous clinical investigations have demonstrated that the effect of statins on peripheral and coronary endothelial function occurs within 24 hours to several months. O'Driscoll et al demonstrated that 4-week simvastatin treatment improved FMD in subjects with dyslipidemia.<sup>5</sup> A similar positive effect on microvascular function was recently confirmed by Nonogaki et al using RH-PAT 4 weeks after pitavastatin therapy.<sup>6</sup> Tsunekawa et al reported that cerivastatin improved



**Figure 2** RH-PAT index before and after treatment in the pitavastatin group (left), rosuvastatin group (middle), and control group (right).

**Notes:** Values are expressed as means (standard deviation). *P*-values represent the results of one-way analysis of variance before and after treatment, respectively. \*denotes  $P < 0.05$  versus the corresponding parameter before treatment.

**Abbreviations:** CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RH-PAT, reactive hyperemia peripheral arterial tonometry.

FMD within 3 days in subjects with diabetes, independent of its lipid lowering effect.<sup>7</sup> Wassmann et al, who measured coronary flow reserve, also showed that endothelial-dependent coronary vasomotion increased 24 hours after a single treatment of pravastatin in subjects with CAD.<sup>8</sup> The present study demonstrated that pitavastatin improved microvascular function rapidly, within 2 hours. This finding may indicate the importance of early and new therapeutic approaches with pitavastatin with respect to improved endothelial function contributing to improved cardiovascular outcomes, such as in the settings of acute coronary syndrome and heart failure.

## Potential mechanisms of the difference between pitavastatin and rosuvastatin

The advantage of pitavastatin over rosuvastatin in the rapid improvement of peripheral microvascular function was demonstrated in the present study, as in previous studies. Sakabe et al examined FMD tests 2 and 12 weeks after pitavastatin and atorvastatin, respectively.<sup>9</sup> They found that the short-term effect of pitavastatin was superior to that of atorvastatin. An intravascular ultrasonographic study also reported that the positive effect of pitavastatin on coronary plaques was faster than that seen with atorvastatin.<sup>10</sup>

These results might be explained as follows. First, pitavastatin administered orally reaches a peak plasma concentration ( $C_{max}$ ) in approximately 1 hour. The  $C_{max}$  at a dose of 2 mg pitavastatin is 26.1 ng/mL, which is higher than that of 5 mg rosuvastatin (3.6 ng/mL).<sup>22,23</sup> Faster transfer of the drug to blood vessels may result in increased bioavailability of NO through the inhibition of Rho-kinase in endothelial cells. An experimental study showed that Rho-kinase inhibition rapidly activated Akt/PI3 kinase within 15 to 30 minutes and increased in a concentration-dependent manner.<sup>24</sup> Second, the pleiotropic effects of statins may depend on their lipophilicity. Because the cell membrane consists of lipid bilayers, intracellular pathways and possible effects of statins differ between lipophilic and hydrophilic statins. It has been reported that cerivastatin, a lipophilic statin, was more effective with the respect to endothelial NO synthase expression for 12 hours than rosuvastatin, a hydrophilic statin, in subjects with diabetes.<sup>25</sup> Furthermore, short-term cardiovascular outcomes after acute myocardial infarction were better in subjects with a lipophilic statin than with a hydrophilic statin.<sup>26</sup> Finally, pitavastatin may simply have a stronger effect on endothelial function than other statins. Also, pitavastatin is marginally metabolized by cytochrome

P450 enzymes, and is less dependent on organic anion-transporting polypeptides for its uptake into hepatocytes.<sup>27,28</sup> Such a unique pharmacological profile of pitavastatin might have novel and wide-ranging effects on endothelial function. The present study demonstrated that pitavastatin resulted in rapid improvement of microvascular function. Since endothelial dysfunction is strongly associated with the onset and development of CAD and considerable mortality despite contemporary therapies,<sup>16,29,30</sup> early modification of endothelial function is of crucial importance. The management of CAD in clinical practice could be improved by considering the physicochemical characteristics of statins. Also, a distinctive metabolic pathway of pitavastatin is associated with a favorable drug–drug interaction profile; this supports the use of pitavastatin among the statins currently available.<sup>28,31</sup>

### Study limitations

Several limitations need to be considered. First, the study was initially designed to include 60 subjects (20 subjects in each group). However, because of wider distribution of the RH-PAT index in the rosuvastatin group than in the other groups, 36 subjects were added, randomly assigned to pitavastatin or rosuvastatin groups on the basis of the value of first RH-PAT index. Two subjects with pitavastatin then refused to perform second RH-PAT test due to pain of cuff-inflation. Crossover designed studies with a larger number of subjects would be ideal to assess the acute effect of two different drugs. Another ideal way would be to randomize subjects to the different treatment groups to balance out other factors. Further, although observer variability of RH-PAT values was small, the results of a one-way analysis of variance did not account for observer variability. Second, this study included subjects with CAD, and the application of these results to other populations may be limited. Furthermore, 73 (78%) subjects continued taking one or more antihypertensive drugs during the examinations, such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, which might have altered endothelial function and affected the results of this study.<sup>32,33</sup> Although no correlations were observed between baseline RH-PAT index and medications, the time of intake of these medications might have altered endothelial function and thus affected the results of this study. Third, RH-PAT index was slightly increased even in the control group, which may be due to 2-hour rest and/or circadian variation of endothelial function.<sup>34</sup> The first examination was performed in the morning in all subjects, and this question may be resolved if the subjects were randomly assigned with respect to the time of day when the first study

was done. Finally, a dose of 2.5 mg of rosuvastatin was used because this is the recommended starting dose in Japan. It remains to be seen whether different doses will show results similar to those found in this study. The very rapid increase in the RH-PAT index after pitavastatin administration may be associated with a decrease in oxidative stress, which inactivates NO. Measurement of plasma concentrations of oxidative stress markers, thiobarbituric acid reactive substances, isoprostanes, and 8-hydroxydeoxyguanosine may illuminate the presumed underlying mechanisms of this finding, and nitroglycerin-mediated vasodilation, as a marker of endothelium-independent vasodilation, should be measured in a future study.

### Conclusion

This RH-PAT study demonstrated that single clinical doses of pitavastatin, but not of rosuvastatin, improved peripheral microvascular function within 2 hours in subjects with CAD. These results may support early intervention of statin therapy in the management of CAD and other atherosclerotic diseases.

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### Disclosure

The authors report no conflicts of interest in this work.

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